REMARKS

Claims 1 and 19-31 are pending. The specification has been amended to include information regarding the deposit of ATCC Accession No. 98351 under the Budapest Treaty. The deposit number is referenced in the Preliminary Amendment that was filed with the application on November 28, 2000. A Statement Regarding Budapest Treaty Deposit accompanies this Response. Claims 1, 19, and 21-31 have been amended as suggested by the Examiner to correct inconsistencies and informalities. Claim 21 has also been amended to correct a typographical error. The specification has been amended as suggested by the Examiner to correct inconsistencies and informalities. Substitute drawings have been submitted. No new matter is added by the amendments.

Objections

The specification has been objected to at pages 10-12, 40, 41, 44, 45, and 54 for use of the term "*HKNG* gene" because the terminology is not consistent throughout the specification. As suggested by the Examiner, "*HKNG* gene" has been amended to "*HKNG1* gene."

The specification is objected to at pages 13 and 52-54 for "SEQ ID Nos." As suggested by the Examiner, "SEQ ID Nos." has been amended to "SEQ ID NOS:"

In claim 21, the spacing between the "w" and "herein" has been deleted such that the word reads "wherein."

Examiner objected to the drawings. New drawings have been submitted with this Response.

Applicants believe that the amendments are responsive to the objections raised by the Examiner and respectfully request that the objections be withdrawn.

35 U.S.C. § 112, First Paragraph (Deposit Requirement)

Claim 29 has been rejected under 35 U.S.C. 112, first paragraph, for lack of written description with respect to the deposit information for the clone contained in ATCC Accession Number 98351 that is disclosed in claim 29.

A deposit of ATCC Accession Number 98351 was made under the Budapest Treaty before the filing date of the present application. The specification has been amended to include the required information regarding the deposit. A Statement accompanies this Response stating that the instant invention will be irrevocably and without restriction released to the public upon issuance of the patent.

In view of the amendment to the specification inserting the deposit information, applicants request that the rejection under 35 U.S.C., § 112, first paragraph be withdrawn.

35 U.S.C. § 112, Second Paragraph

Claims 1 and 19-31 have been rejected for indefiniteness.

Claims 1 and 19-31 have been rejected for use of the term "capable of" in step (a) of claim 1 and 19. In keeping with the Examiner's suggestion, claims 1 and 19 has been amended to replace "capable of identifying" in step (a) to "that identifies." Claims 20-31 ultimately depend from claim 1 and incorporate the term "capable of" by virtue of their dependency. Therefore, the amendment claim 1 addresses the rejection for claims 20-31.

Claims 1 and 19-31 have also been rejected for indefiniteness for use of the abbreviation(s) and for lack of proper antecedent basis for the terms "*HKNG1*", "*HKNG*" and "*HGNG.*" As suggested by the Examiner, applicants have amended the claims to consistently recite the term "*HKNG1.*"

Claim 21 has been rejected for indefiniteness because the term "Elisa" is an abbreviation for "enzyme-linked immunosorbent assay" and should be capitalized. As suggested by the Examiner, the term "elisa" has been amended to "enzyme-linked immunosorbent assay (ELISA)."

Applicants submit that in view of the amendments discussed above, the rejection under 35 U.S.C. § 112, second paragraph should be withdrawn, which action is requested.

Double Patenting

Claims 1 and 19-31 have been provisionally rejected under for obviousness-type double patenting over claims 1-9 of co-pending Application No. 09/236,134. Applicants will submit a Terminal Disclaimer upon notification that pending claims are allowable.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicants believe that all claim are now in condition for allowance, which action is respectfully requested. Enclosed is a $930 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket no. 07334-362001.

Respectfully submitted,

Date: January 21, 2003

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Version with markings to show changes made

In the specification:

The paragraph beginning at page 10, line 5 has been amended as follows:

The term "allelic variant of a polymorphic region of an [*HKNG*] *HKNG1* gene" refers to a region of an [*HKNG*] *HKNG1* gene having one of several nucleotide sequences found in that region of the gene in other individuals, as well as to polypeptides encoded by nucleic acid molecules comprising said sequences.

The paragraph beginning at page 10, line 30 and continuing on p. 11 has been amended as follows:

A "delivery complex" shall mean a targeting means (*e.g.*, a molecule that results in higher affinity binding of a gene, protein, polypeptide or peptide to a target cell surface and/or increased cellular uptake by a target cell). Examples of targeting means include: sterols (*e.g.*, cholesterol), lipids (*e.g.*, a cationic lipid, virosome or liposome), viruses (*e.g.*, adenovirus, adeno-associated virus, and retrovirus) or target cell specific binding agents (*e.g.*, ligands recognized by target cell specific receptors). Preferred complexes are sufficiently stable *in vivo* to prevent significant uncoupling prior to internalization by the target cell. However, the complex is cleavable under appropriate conditions within the cell so that the gene, protein, polypeptide or peptide is released in a functional form. It is also possible that soluble forms of the protein also exist. Such soluble isoforms can arise through variable splicing of the [*HKNG*] HKNG1 gene or alternatively as a result of proteolysis of a membranous isoform.

The paragraph beginning at page 11, line 10 has been amended as follows:

As is well known, genes for a particular polypeptide may exist in single or multiple copies within the genome of an individual. Such duplicate genes may be identical or may have certain modifications, including nucleotide substitutions, additions or deletions, which all still code for polypeptides having substantially the same activity. The term "DNA sequence encoding an [HKNG] HKNG1 polypeptide" may thus refer to one or more genes within a

particular individual. Moreover, certain differences in nucleotide sequences may exist between individual organisms, which are called alleles. Such allelic differences may or may not result in differences in amino acid sequence of the encoded polypeptide yet still encode a protein with the same biological activity.

The paragraph beginning at page 11, line 19 has been amended as follows:

As used herein, the term "gene" or "recombinant gene", as applied to [*HKNG*] *HKNG1*, refers to a polynucleotide or nucleic acid molecule comprising an open reading frame encoding one of the [HKNG] HKNG1 polypeptides of the present invention. In one embodiment, these terms relate to a cDNA sequence including, but not limited to, a polynucleotide or nucleic acid sequence obtained via reverse transcription of an mRNA molecule. In one embodiment, the term nucleic acid or polynucleotide is a nucleic acid molecule which is not genomic but is a cDNA derived from a contiguous coding region which includes, but is not limited to, reverse transcribed cDNA. In another embodiment, the term nucleic acid or polynucleotide refers to a nucleic acid molecule which comprises contiguous nucleotide codons. In yet another embodiment, the term nucleic acid or polynucleotide is a nucleic acid molecule which is genomic but which excludes intronic sequences.

The paragraph beginning at page 12, line 10 has been amended as follows:

Furthermore, a degree of homology or similarity of amino acid sequences is a function of the number of conserved amino acids at positions shared by the amino acid sequences. A sequence which is "unrelated" or "non-homologous" with one of the human [*HKNG*] HKNG1 sequences of the present invention typically is a sequence which shares less than 40 % identity, though preferably less than 25 % identity with one of the human [*HKNG*] HKNG1 sequences of the present invention.

The paragraph beginning at page 13, line 21 has been amended as follows

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75% or more) identical to each other typically remain hybridized to each other.

Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 2.0 X SSC at 50° C. (low stringency) or 0.2 X SSC, 0.1% SDS at 50-65°C (high stringency). In one embodiment, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of [SEQ ID Nos.] SEQ ID NOS:1, 3, 5, 6, or 7, or to a complement thereof, corresponds to a naturally-occurring nucleic acid molecule.

The paragraph beginning at page 14, line 23 has been amended as follows:

FIG. [3A-3R.] 3A-3II. Genomic sequences of the human *HKNG1* gene [(SEQ ID NO.7)] (SEQ ID NO:7). Exons are in bold and the 3' and 5' UTR's are underlined.

The paragraph beginning at page 14, line 25 has been amended as follows:

FIG. [4.] 4A-4B. Summary of [in situ] *in situ* hybridization analysis of *HKNG1* mRNA distribution in normal human brain tissue.

The paragraph beginning at page 40, line 5 has been amended as follows:

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. Accordingly, nucleic acid molecules described herein or fragments thereof, can be used to map the location of the corresponding genes on a chromosome. For example, the nucleic acid molecules described herein can be used to map the chromosomal location of [*HKNG*] *HKNG1* homologues in various species. Such mapping information can be used, for example, for analysis of the activity of [*HKNG*] *HKNG1* transgenes in mice. The nucleic acid molecules can further be used to map the location of copies of [*HKNG*] *HKNG1* genes in the human chromosome, such as those caused by genetic abnormalties, e.g., translocations.

The paragraph beginning at page 41, line 10 has been amended as follows:

In another embodiment, a [*HKNG*] HKNG1 polypeptide and fragments and sequences thereof and antibodies specific thereto can be used to map the location of the gene encoding the polypeptide on a chromosome. This mapping can be carried out by specifically detecting the presence of the polypeptide in members of a panel of somatic cell hybrids between cells of a first species of animal from which the protein originates and cells from a second species of animal and then determining which somatic cell hybrid(s) expresses the polypeptide and noting the chromosome(s) from the first species of animal that it contains. For examples of this technique, see Pajunen *et al.* (1988*) Cytogenet. Cell Genet. 47*:37-41 and Van Keuren *et al.* (1986*) Hum. Genet. 74*:34-40. Alternatively, the presence of the polypeptide in the somatic cell hybrids can be determined by assaying an activity or property of the polypeptide, for example, enzymatic activity, as described in Bordelon-Riser *et al.* (1979*) Somatic Cell Genetics 5*:597-613 and Owerbach *et al.* (1978*) Proc. Natl. Acad. Sci. USA 75*:5640-5644.

The heading beginning at page 44, line 13 has been amended as follows:

USE OF [*HKNG*] *HKNG1* GENE SEQUENCES IN PREDICTIVE MEDICINE

The paragraph beginning at page 44, line 15 has been amended as follows:

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining [HKNG] HKNG1 protein and/or nucleic acid expression as well as [HKNG] HKNG1 activity, in the context of a biological sample (e.g., blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant or unwanted [HKNG] HKNG1 expression or activity. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with an [HKNG] HKNG1 protein, nucleic acid expression or activity. For example, mutations in an [HKNG] HKNG1 gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset

of a disorder characterized by or associated with an [HKNG] HKNG1 protein, nucleic acid expression or activity.

The paragraph beginning at page 44, line 29 has been amended as follows:

As an alternative to making determinations based on the absolute expression level of selected genes, determinations may be based on the normalized expression levels of these genes. Expression levels are normalized by correcting the absolute expression level of an [*HKNG*] *HKNG1* gene by comparing its expression to the expression of a gene that is not an [*HKNG*] *HKNG1* gene, e.g., a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene. This normalization allows the comparison of the expression level in one sample, e.g., a patient sample, to another sample, e.g., a non-BAD-affected normal sample, or between samples from different sources.

The paragraph beginning at page 45, line 6 has been amended as follows:

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a gene, the level of expression of the gene is determined for 10 or more samples of different cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The cell isolates are selected depending upon the tissues in which the gene of interest is expressed. For example, for [HKNG] HKNG1 family members, expression was observed in the brain. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the gene(s) in question. The expression level of the gene determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that gene. This provides a relative expression level and aids in identifying extreme cases of a [HKNG] HKNG1-mediated disease.

The paragraph beginning at page 45, line 18 has been amended as follows:

For example, by way of illustration only, for [HKNG] HKNG1 family members, diseases which may be studied include, without limitation, those associated with tissues of the brain.

The paragraph beginning at page 45, line 21 has been amended as follows:

Preferably, the samples used in the baseline determination will be from an [HKNG] HKNG1-mediated diseased or from non-diseased cells of tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the [HKNG] *HKNG1* gene assayed is cell-type specific for the tissues in which expression is observed versus the expression found in normal cells. Such a use is particularly important in identifying whether an [*HKNG*] *HKNG1* gene can serve as a target gene. In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from brain cells provides a means for grading the severity of the [HKNG] HKNG1-mediated disease state.

The paragraph beginning at page 45, line 31 has been amended as follows:

Another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs, compounds) on the expression or activity of [HKNG] HKNG1 in clinical trials.

The paragraph beginning at page 52, line 3 has been amended as follows:

Accordingly, in one aspect, the invention provides substantially purified antibodies or fragment thereof, and non-human antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence selected from the group consisting of: the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4; a fragment of at least 15 amino acid residues of the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, an amino acid sequence which is at least 95% identical to the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4; and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the nucleic acid molecule consisting of any one of [SEQ ID Nos.] SEQ ID NOS:1, 3, 5, 6, or 7, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at

65°C. In various embodiments, the substantially purified antibodies of the invention, or fragments thereof, can be human, non-human, chimeric and/or humanized antibodies.

The paragraph beginning at page 52, line 18 has been amended as follows:

In another aspect, the invention provides non-human antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence selected from the group consisting of: the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4; a fragment of at least 15 amino acid residues of the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, an amino acid sequence which is at least 95% identical to the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4; and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the nucleic acid molecule consisting of any one of [SEQ ID Nos.] SEQ ID NOS:1, 3, 5, 6, or 7, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies.

The paragraph beginning on page 53, line 1 has been amended as follows:

In still a further aspect, the invention provides monoclonal antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence selected from the group consisting of: the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4; a fragment of at least 15 amino acid residues of the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, an amino acid sequence which is at least 95% identical to the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4; and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the

nucleic acid molecule consisting of any one of [SEQ ID Nos.] SEQ ID NOS:1, 3, 5, 6, or 7, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The paragraph beginning at page 53, line 15 has been amended as follows:

The substantially purified antibodies or fragments thereof specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain cytoplasmic membrane of a polypeptide of the invention. In one embodiment, the substantially purified antibodies or fragments thereof, the human or non-human antibodies or fragments thereof, and/or the monoclonal antibodies or fragments thereof, of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequence of [SEQ ID Nos.] SEQ ID NOS:2 or 4.

The paragraph beginning at page 54, line 1 has been amended as follows:

Still another aspect of the invention is a method of making an antibody that specifically recognizes [HKNG] HKNG1, the method comprising immunizing a mammal with a polypeptide. The polypeptide used as an immungen comprises an amino acid sequence selected from the group consisting of: the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4; a fragment of at least 15 amino acid residues of the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, an amino acid sequence which is at least 95% identical to the amino acid sequence of any one of [SEQ ID Nos.] SEQ ID NOS:2 or 4, wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4; and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the nucleic acid molecule consisting of any one of [SEQ ID Nos.] SEQ ID NOS:1, 3, 5, 6, 7, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. After immunization, a sample is collected from the mammal that contains an antibody that specifically recognizes a [HKNG] HKNG1 polypeptide as exemplified in [SEQ ID Nos.] SEQ ID NOS:2 or 4, or portions thereof. Preferably, the polypeptide is recombinantly produced using

a non-human host cell. Optionally, the antibodies can be further purified from the sample using techniques well known to those of skill in the art. The method can further comprise producing a monoclonal antibody-producing cell from the cells of the mammal. Optionally, antibodies are collected from the antibody-producing cell.

The following paragraphs have been added before the paragraph beginning on page 87, line 24:

Under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure, deposit of the following materials was made with the American Type Culture Collection (ATCC) of Rockville, MD, USA.

Applicants' assignees, Millennium Pharmaceuticals, Inc. and The University of California, represent that the ATCC is a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. All restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent. The material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. § 122. The deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited plasmid, and in any case for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. Applicants' assignee acknowledges its duty to replace the deposit should the depository be unable to replace the deposit or should the depository be unable to furnish a sample when requested due to the condition of the deposit.

The clone of human DNA, Bluescript Epfsh 15w6, was deposited with the American Type Culture Collection (ATCC, Rockville, MD); received by the ATCC on March 6, 1997; and was assigned ATCC designation 98351.

In the claims:

Claims 1, 19, and 21-31 and have been amended as follows:

1. (Amended) A method for identifying an individual having or at risk of developing a neuropsychiatric disorder comprising the step of detecting the presence or absence of *HKNG1* gene product in a patient sample wherein said method comprises the steps of:

a) incubating a sample in the presence of a detectably labeled antibody [capable of identifying] that identifies the [*HKNG*] *HKNG1* gene product; and

b) assaying for the presence or absence of the [*HGNG*] *HKNG1* gene product, wherein the presence of a human *HKNG1* gene product indicates that the individual has or is at risk of developing a bipolar affective disorder or schizophrenia.

19. (Amended) A method of identifying an individual having or at risk of developing a bipolar affective disorder or schizophrenia comprising the step of detecting the presence or absence of a *HKNG1* gene product in a patient sample wherein said method comprises the steps of:

a) incubating a sample in the presence of a detectably labeled antibody [capable of identifying] that identifies the [*HKNG*] *HKNG1* gene product; and

b) assaying for the presence or absence of the [*HGNG*] *HKNG1* gene product, wherein the presence of aberrant level of the human *HKNG1* gene product indicates that the individual has or is at risk of developing a bipolar affective disorder or schizophrenia.

20. (Reiterated) The method according to Claim 1, wherein said assay step comprises an immunoassay.

21. (Amended) The method according to Claim 1, [w herein] wherein said immunoassay is an [Elisa] enzyme-linked immunosorbant assay (ELISA).

22. (Amended) The method according to Claim 1, where said [*HGNG*] *HKNG1* gene product is detected in a blood, serum, lymph, or thoracentesis sample.

23. (Amended) The method according to Claim 1, wherein said [*HGNG*] *HKNG1* gene product is detected in cerebrospinal fluid.

24. (Amended) The method according to Claim 1, wherein said [*HGNG*] *HKNG1* gene product is detected *in situ* in a histological specimen.

25. (Amended) The method according to Claim 24, wherein said [*HGNG*] *HKNG1* gene product is detected on the surface of a cell.

26. (Amended) The method according to Claim 1, wherein said [*HKNG*] *HKNG1* product is a conserved variant or peptide fragment thereof.

27. (Amended) The method of Claim 1, wherein said [*HKNG*] *HKNG1* gene product comprises an amino acid sequence which is different from the amino acid sequence depicted in SEQ ID NO:2.

28. (Amended) The method of Claim 1, wherein said [*HKNG*] *HKNG1* gene product comprises an amino acid sequence which is different from the amino acid sequence depicted in SEQ ID NO:4.

29. (Amended) The method according to Claim 1, wherein said [*HKNG*] *HKNG1* gene product comprises the amino acid sequence encoded by a nucleic acid molecule that hybridizes under highly stringent conditions to the nucleic acid insert of the clone contained in ATCC accession No. 98351, wherein said stringent conditions comprise hybridization in 0.5 M $NaHPO_4$, 7% SDS, 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1%SDS at 68°C.

30. (Amended) The method of Claim 29, wherein said [*HKNG*] *HKNG1* gene product comprises the amino acid sequence of SEQ ID NO:2 with a substitution of a lysine for a glutamic acid at amino acid residue 202 of SEQ ID NO:2.

31. (Amended) The method of Claim 29, wherein said [*HKNG*] *HKNG1* gene product comprises the amino acid sequence of SEQ ID NO:4 with a substitution of a lysine for a glutamic acid at amino acid residue 184 of SEQ ID NO:4.

New drawings replacing Figs. 1-5 have been submitted.